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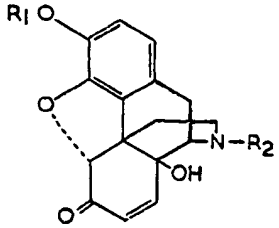
(54) PROCESS FOR THE PREPARATION OF NORMORPHINE DERIVATIVES

(71) We, SANKYO COMPANY LIMITED, a Japanese Body Corporate, of No. 1—6, 3-chome, Nihonbashi Hon-cho, Chyuo-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel process for the preparation of 14-hydroxy-normorphinone derivatives. More particularly, it relates to a novel process for the preparation of 14 - hydroxy - normorphinone derivatives having the formula



(I)

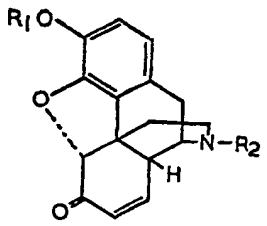
wherein R_1 and R_2 may be the same or different and each represents an alkyl group having from 1 to 4 carbon atoms, an allyl group or an aralkyl group.

Heretofore, 14 - hydroxy - codeinone has been produced by subjecting thebaine obtained from natural products to oxidation. However, in this process only a small amount of thebaine can be obtained from the natural products.

A process for preparing 14-hydroxy-codeinone from codeinone is also disclosed in the Journal of the American Chemical Society, vol. 89, p.1942 (1967) and the Chemistry of the Morphine Alkaloids. Oxford, London, 1954, p.125. According to the process described in this literature, 14-hydroxy-codeinone is prepared by reducing codeinone to produce dihydro-codeinone, reacting the latter compound with dimethyl sulfate in the presence of an alkali to produce dihydro-codeinone enol methyl ester, reacting the latter compound with methyl hypobromite to produce 7-bromo-dihydro-codeinone dimethyl ketal, reacting the latter compound with pyridine to produce codeinone dimethyl ketal, reacting the latter compound with phosphorus trichloride to produce thebaine and then oxidizing the latter compound. However, this process is not suitable for commercial production, because it needs a large number of steps and the total yield is only about 20%.

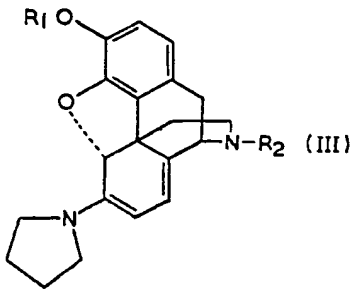
Accordingly, it is an object of this invention to provide a new process for preparing 14-hydroxy-normorphinone derivatives from normorphinone derivatives which can be obtained in large amounts from natural product with a small number of steps and good yield.

It has been found that 14-hydroxy-normorphinone derivatives of the above formula (I) can be prepared by a process which comprises (a) heating a normorphinine derivative having the formula



(II)

wherein R_1 and R_2 are as defined above with pyrrolidine in ahe molar ratio of one to one in the presence of an aprotic solvent to produce a normorphinone pyrrolidinyl enamine having the formula

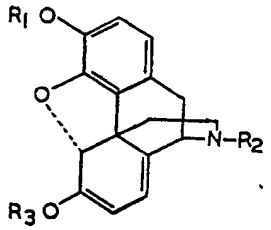


(III)

wherein R_1 and R_2 are as defined above and oxidizing the latter compound or (b) reacting a normorphinone derivative of the above formula (II) with an alcohol having the formula

$$R_3OH \qquad (IV)$$

wherein R_3 represents an alkyl group having from 1 to 4 carbon atoms or an alkoxyalkyl group
in the presence of an aprotic solvent and an aromatic sulfonic acid to produce a normorphinone enol ether having the formula



(V)

wherein R_1, R_2 and R_3 are as defined above and oxidizing the latter compound.

In the above formulae, the alkyl group can be a straight or branched alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

An example of the aralkyl group is a phenylalkyl group such as benzyl or phenethyl. Examples of the alkoxyalkyl group are methoxymethyl, ethoxymethyl, methoxyethyl and ethoxyethyl.

All the 14-hydroxy-normorphinone derivatives of the formula (I) are useful as intermediates for the synthesis of known 14-hydroxy-morphinone derivatives, such as N-phenethyl - 14 - hydroxy - dihydro - normorphinone, 14 - hydroxy - dihydro - morphinone, N - allyl - 14 - hydroxy - dihydro - normorphinone or 14 - hydroxy - dihydro - 6β-thebainol 4-methyl ether, which are known as analgesic morphine antagonists and antitussives (Textbook of Organic Medicinal and Pharmaceutical Chemistry, 4th Ed. (1966) p.662). For example, N-phenethyl-14-hydroxy-dihydro-morphinone is produced by subjecting N - phenethyl - 14 - hydroxy - normorphinone to catalytic reduction.

According to the present invention, 14-hydroxy-normorphinone derivatives can be prepared with only two steps and the total yield is about 20—40%, so that the process of this invention is suitable for a commercial process.

The use of more than one mole of pyrolidine per mole of said compound (II) is not desirable because of the formation of 7-pyrrolidine-dihydro-normorphinone.

As the aprotic solvent, there may be satisfactorily employed any organic solvent which will not provide protons. It is desirable to employ an organic solvent which forms an azeotrope with water, for example, hydrocarbons such as benzene or toluene, or halogenated hydrocarbons such as methylene chloride, chloroform or carbon tetrachloride.

The reaction temperature is generally above room temperature and preferably at about 60—80°C. The removal of the water produced in the reaction by azeotropy shortens the reaction period and improves the yield. It is advantageous to conduct the reaction at the reflux temperature of an aprotic solvent boiling at about 60—80°C., while the water formed during the reaction is removed by azeotropy. The reaction period is usually from about one hour to 3 hours. It is found that addition of a catalytic amount of an aromatic sulfonic acid, such as p-toluenesulfonic acid or benzenesulfonic acid, accelerates the reaction.

After completion of the reaction, the desired product (III) may be easily recovered from the reaction mixture by conventional means. For instance, the reaction mixture is washed with water and dried over anhydrous sodium sulfate.

Where an aromatic sulfonic acid is employed as catalyst the reaction mixture is washed with a dilute aqueous alkali solution and water and dried over anhydrous sodium sulfate.

The dried reaction mixture is decolored with active carbon or active alumina after concentration and then the solvent is distilled off.

If desired, the crude product thus obtained may be purified by recrystallization from a suitable solvent such as isopropanol. The reaction is carried out with quantative yields and does not produce by-products. Therefore, the crude product can be employed in the next step without further purification.

In the preparation of compound (I) from the compound (III), the reaction may preferably be carried out by subjecting the compound (III) to oxidation in the presence of a solvent.

The oxidation is carried out by employing an oxidizing agent such as hydrogen peroxide, chromic acid, potassium permanganate or an organic peracid, for example, peracetic acid or perbenzoic acid. Most preferably a 30%

aqueous hydrogen peroxide solution is employed. As the solvent, there may be satisfactorily employed an acid, for example, phosphoric acid, formic acid, acetic acid, or a halogenated acetic acid such as chloroacetic acid, or an organic solvent such as acetone.

It is advantageous to carry out the oxidation reaction in the presence of as little water as possible, in order to obtain good yields. The reaction temperature is not critical, but it is preferable to conduct the reaction at a temperature of about 40—60°C. The reaction period also is not critical and it may be varied depending upon the kind of the solvent employed. Generally the reaction period is from about 30 minutes to 2 hours.

After completion of the reaction, the desired product (I) may be recovered from the reaction mixture by conventional means. For instance, the reaction mixture is diluted with water and made alkaline with aqueous ammonia. The alkaline mixture is extracted with a suitable solvent, such as chloroform, and the extract is washed with water and dried over anhydrous sodium sulfate. The solvent is then distilled off from the extract. If desired, the crude product thus obtained may be purified by washing with ethanol or recrystallizing from ethanol.

In the preparation of compound (V) from compound (II), the reaction may preferably be carried out by reacting compound (II) with compound (IV) in the presence of an aprotic solvent and an aromatic sulfonic acid. In this step, there can be used the same aprotic solvent and aromatic sulfonic acid as those employed for the preparation of compound (III) from compound (II). It is preferable to employ more than one mole of the alcohol (IV) per mole of said normorphinone (II).

The reaction temperature is usually above about 60°C. It is preferable to conduct the reaction at the reflux temperature of an aprotic solvent boiling at 60—80°C.

The removal of the water produced in the reaction by azeotropy shortens the reaction period and improves the yield. The reaction period is usually from about 3 hours to 15 hours.

After completion of the reaction, the desired product (V) may be easily recovered from the reaction mixture by conventional means. For instance, the reaction mixture is neutralized by addition of an aqueous alkali solution, such as aqeous sodium hydroxide, under cooling with ice and the organic phase is separated. The organic phase is washed with water and the desired product is extracted with dilute aqueous acetic acid. The extract is treated with hydroxylamine hydrochloride to convert any by-product (keto-compound) contaminating the extract to the corresponding oxime compound. The resulting extract, optionally after decoloration with active carbon, is made strongly alkaline by addition of a concentrated aqueous caustic alkali solution and extracted with benzene. The benzene extract is washed with water and dried over anhydrous sodium sulfate, and then the solvent is distilled off. The residue is recrystallized from a suitable solvent such as ethanol and, if desired, purified by chromatography.

In carrying out the preparation of compound (I) from compound (V), the reaction may preferably be carried out in the same manner as that employed for the preparation of compound (I) from compound (III). In this step, the presence of water is preferable, because it facilitates control of the exothermic reaction.

The compounds having the formula (II) in which both R_1 and R_2 are the above-defined groups other than methyl are novel and can be prepared by known processes, e.g. subjecting normorphinone to alkylation, benzylation or aralkylation.

The following examples are given for the purpose of illustrating of this invention.

Example 1.

14-Hydroxy-codeinone

(1)—1. To a solution of 1.5g of codeinone in 20ml. of benzene was added 0.5ml. of pyrolidinine. The resulting mixture was heated under reflux for 1.5 hours, while the water produced was distilled off as an azeotropic mixture with benzene.

After completion of the reaction, the reaction mixture was cooled, washed twice with water and dried over anhydrous sodium sulfate. The reaction solvent was distilled off to produce an oily orange residue.

The residue dissolved in benzene was chromatographed through .a column charged with 30g. of active alumina and eluted with benzene.

The eluates were collected and the solvent was distilled off. The residue was washed with isopropanol and recrystallized from isopropanol to give 2.0g. of pale yellow crystals of codeinone pyrrolidinyl enamine melting at 126—128°C.

Analysis:		
Calculated for $C_{22}H_{26}N_2O_2$;		C, 75.40; H, 7.48; N, 7.99
Found:		C, 75.14; H, 7.74; N, 7.90
IR(Nujol);		γc=C 6.35μ
UV:		λ_{max}^{EtOH} 336 mμ (ε=8450)

(1)—2. To a solution of 9g. of codeinone in 80ml. of benzene were added 3ml. of pyrrolidine and 0.3g. of p-toluenesulfonic acid monohydrate. The resulting mixture was heated under reflux for 1.5 hours, while the water produced was distilled off by azeotropy with benzene. After completion of the reaction, the reaction mixture was cooled, washed with two 15ml. portions of a 10% aqueous sodium carbonate solution and next with two 20ml. portions of water, and dried over anhydrous sodium sulfate.

The dried mixture was treated in the same manner as in the above (1)—1 to give 9.8g. of codeinone pyrrolidynyl enamine.

(2) To a solution 2.5g. of codeinone pyrrolidinyl enamine in 5.5ml. of 98% aqueous formic acid was added 1ml. of a 30% aqueous hydrogen peroxide solution. The temperature of the mixture rose to about 46°C and then fell slowly to room temperature. After about 50 minutes, the reaction mixture was diluted with 20ml. of ice water, cooled at 0°C and neutralized by addition of anhydrous sodium carbonate. The mixture was made alkaline by addition of ammonia and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was washed with methanol to give 0.95g. of crystals of 14-hydroxy-codeinone melting at 270—275°C. The product thus obtained was identified with an authentic specimen by means of a mixed melting point and infrared spectra.

Example 2

14-Hydroxy-benzylmorphinone

(1) To a solution of 2.0g. of benzylmorphinone in 60ml. of benzene were added toluenesulfonic acid monohydrate. The resulting mixture was heated under reflux for 1.5 hours, while the water produced was distilled off as an azeotropic mixture with benzene. After completion of the reaction, the reaction mixture was treated in the same manner as in the above Example 1 (1)—2 to give 1.85 g. of benzylmorphinone pyrrolidinyl enamine as a yellow oil.

Analysis:
Calculated for $C_{25}H_{30}N_2O_2$ C. 78.84; H. 7.09; N. 6.57
Found: C. 78.95; H. 7.17; N. 6.34
IR(Nujol): $\gamma c=C$ 6.35μ
UV: λ_{max}^{EtOH} 335mμ (ε=9375)

By the same procedure as Example 2 (1), the following normorphinone pyrrolidinyl enamine compounds were produced from the corresponding normorphinone derivatives in good yields.

N - phenethyl - norcodeinone pyrrilidinyl enamine
m.p. 153.5—155.5°C.

N - methyl - normorphinone 3 - allyl ether pyrrolidinyl enamine
Pale red oil
IR(Nujol): $\gamma c=C$ 6.3μ
UV: λ_{max}^{EtOH} 335mμ

N-allyl norcodeinone pyrrolyidinyl enamine
Pale orange oil
IR(Nujol): $\gamma c=C$ 6.3μ
UV: λ_{max}^{EtOH} 335mμ

(2) To a solution of 1.6g. of benzylmorphinone pyrrolidinyl enamine in 3.2ml. of a 98% aqueous formic acid solution were added 0.6ml. of a 30% aqueous hydrogen peroxide solution. The resulting mixture was left at room temperature for about one hour. After completion of the reaction, the reaction mixture was treated in the same manner as in the above Example 1 (2) to give 0.5g. of crystals of 14 - hydroxy - benzylmorphinone melting at 244—245°C.

Analysis:
Calculated for $C_{21}H_{23}NO_4$
C, 74.02; H, 5.95; N, 3.60
Found
C, 73.62; H, 6.41; N, 3.58

By the same procedure as Example 2 (2), the following 14 - hydroxy - normorphinone derivatives were produced from the corresponding normorphinone pyrrolidinyl enamine in good yields.

14 - Hydroxy - N - phenethyl - norcodeinonne tartrate
m.p. 198°C (with decomposition)
14 - Hydroxy - N - methyl - normorphinone 3 allyl ether
m.p. 222—223°C
14-Hydroxy-N-allyl-norcodeinine
m.p. 133—135°C

EXAMPLE 3

14-Hydroxy-ethylmorphinone

(1) To a solution of 4.5g. of codeinone in 60ml. of benzene were added 2.0ml. of pyrrolidine and 0.2g. of p-toluenesulfonic acid. The resulting mixture was heated under reflux for 1.5 hours, while the water produced was distilled off as an azeotropic mixture with benzene. After completion of the reaction, the reaction solvent was distilled off to produce 3.3g. of oily crude ethylmorphinone pyrrolidinyl enamine.

IR (Nujol): $\gamma c=C$ 6.35μ
UV: λ_{max}^{EtOH} 335mμ

(2) To a solution of 3.3g. of crude ethylmorphinone pyrrolidinyl enamine in 7.8ml. of a 98% aqueous formic acid solution were added 1.45ml. of a 30% aqueous hydrogen peroxide solution. The resulting mixture was left at room temperature for about one hour. After completion of the reaction, the reaction mixture was treated in the same manner as in the above Example 1 (2) to give 1.0g. of crystals of 14 - hydroxy - ethyl - morphinone melting at 236—237°C.

Analysis:
Calculated for $C_{19}H_{21}NO_4$;
C, 69.70; H, 6.47; N, 4.28
Found:
C, 69.84; H, 6.37; N, 4.25

By the same procedure as Example 3 (1) and (2), the following 14-hydroxy-normorphinone derivatives were produced from the corresponding normorphinone derivatives in good yields.

14 - Hydroxy - N - methyl - normorphinone 3-isopropyl ether
m.p. 218—219°C.
14 - Hydroxy - N - methyl - normorphinone 3-n-propyl ether
m.p. 237—239°C.

EXAMPLE 4

14-Hydroxy-benzylmorphinone

(1) A mixture of 5.3g. of p-toluenesulfonic acid monohydrate and 160ml. of benzene was heated under reflux for 1.5 hours to completely remove water by the formation of an azeotropic mixture.

After cooling, the resulting mixture, 40ml. of n-propanol and 8g. of benzylmorphinone were dissolved therein.

The resulting mixture was heated under reflux for 3.5 hours. While the water produced was distilled off.

After completion of the reaction, the reaction mixture was cooled with ice and washed twice with a mixture of 5ml. of a 30% aqueous sodium hydroxide solution and 25ml. of water, washed twice with water and then extracted with 10% aqueous acetic acid. After the extract was washed with benzene, 0.5g. of hydroxylamine hydrochloride was added to the extract and heated at 50—60° C for 10 minutes to convert a keto-compound contaminating the extract to the corresponding oxime compound.

The extract was decolored with active carbon, adjusted to above pH 12.0 by addition of a 30% aqueous sodium hydroxide solution and extracted with benzene. The benzene extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off.

The residue was dissolved in a small amount of benzene and adsorbed on an alumina column. The colum was eluted with benzene. The benzene eluate was collected and the solvent was distilled off.

The residue was dissolved in a mixture of 20ml. of ethanol and 1ml. of water. To the solution was added 1g. of tartaric acid with agitation to give 1.4g. of benzylmorphinone enol n-propyl ether tartrate as crystals melting at 118—123°C (with decomposition).

Analysis
Calculated for $C_{31}H_{35}NO_9 \cdot 1.5H_2O$
C, 62.83; H, 6.46; N, 2.36
Found:
C, 62.95; H, 6.48; N, 2.23

By the same procedure as Example 4 (1), the following normorphinone enol ethers were produced from the corresponding normorphinone derivatives in good yields.

Codeinone enol n-butyl ether
m.p. 103—104°C.
UV. λ_{max}^{EtOH} 285μ (ε=8228)
Codeinone enol n-propyl ether
m.p. 155.5—156.6°C.
UV. λ_{max}^{EtOH} 288mμ (ε=7870)
Codeinone enol ethyl ether
m.p. 123—124°C.
UV. λ_{max}^{EtOH} 285mμ (ε=7819)
Codeinone enol-isopropyl ether
m.p. 131—132°C
UV. λ_{max}^{EtOH} 286mμ (ε=8118)

Codeinone 2-methoxyethyl ether
m.p. 140—142°C
UV. λ_{max}^{EtOH} 284mμ (ε=7333)

(2) To a solution of 2.9g. of benzylmorphinone enol n-propyl ether tartrate in a mixture of 1.75ml. of a 85% aqueous formic acid solution and 2.5ml. of water were added 0.7ml. of a 30% aqueous hydrogen peroxide solution. The resulting mixture was left at 50°C. for 1.5 hours. After completion of the reaction, ice water was added to the reaction mixture and the mixture was made alkaline by adition of an aqueous ammonia solution and extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off. The pale brown residue was washed with methanol to give 1.7g. of 14-hydroxy-benzyl morphinone as crystals melting at 244—245°C.

Analysis:
Calculated for $C_{24}H_{25}NO_4$;
C, 74.02; H, 5.95; N, 3.60
Found:
C, 73.62; H, 6.41; N, 3.58

By the same procedure as Example 4 (2), 14-hydroxy-codeinone was produced from codeinone enol-n-butyl ether, codeinone enol n-propyl ether, codeinone enol ethyl ether, codeinone enol isopropyl ether and codeinone 2-methoxyethyl ether in good yields.

WHAT WE CLAIM IS:—

1. A process for preparing a 14-hydroxy-normorphinone derivative of formula (I) (as herein defined), which comprises heating a normorphinone derivative of formula (II) (as herein defined) with a substantially equimolar amount of pyrrolidine in the presence of an aprotic solvent, to produce a normorphinone pyrrolidinyl enamine of formula (III) (as herein defined), and oxidizing said compound of formula (III) to produce said compound of formula (I).

2. A process according to claim 1, in which the reaction between said compound of formula (II) and pyrrolidine is conducted in the presence of an aromatic sulfonic acid.

3. A process for preparing a 14-hydroxy-normorphinone derivative of formula (I) (as herein defined), which comprises reacting a normorphinone derivative of formula (II) (as heretin defined) with an alcohol of formula R_3OH (wherein R_3 is an alkyl group having from 1 to 4 carbon atoms or an alkoxyalkyl group) in the presence of an aprotic solvent and an aromatic sulfonic acid, to produce a normorphinone enol ether of formula (V) (as herein defined), and oxidizing said compound of formula (V) to produce said compound of formula (I).

4. A process according to claim 2 or claim 3, in which said aromatic sulfonic acid is p-toluene sulfonic acid.

5. A process according to any preceding claim, in which said aprotic solvent is benzene.

6. A process according to any preceding claim, in which the oxidation is effected by the use of hydrogen peroxide.

7. Compounds of formula (I) (as herein defined) when prepared by the process of any preceding claim.

MARKS & CLERK

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